was removed. The resulting solution was concentrated under reduced pressure. During the concentration, crystals separated and were collected. After recrystallization from water the 2,4-diacetamidophenol[5] melted at 222–225° (micro-block).

2,4-Diacetamidophenyl Acetate.—After the crystals, which collected during concentration of the solution from the reduction, had been removed the remaining solution was concentrated to dryness under reduced pressure at 60–80°. The resulting material was recrystallized first from methanol, then to constant melting point from water. The 2,4-diacetamidophenyl acetate[5] melted at 187–190° (micro-block).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.63; H, 5.52; N, 11.05.

5-Acetamido-2-methylbenzoxazole.—A 342-mg. sample of 2,4-diacetamidophenyl acetate was heated in a bomb tube at 350° for one hour. The product was a semicrystalline dark mass possessing the odor of acetic acid. This material was dissolved in warm ethyl acetate, decolorized with Darco G-60 and evaporated to dryness. The faintly buff-colored crystalline product weighed 250 mg. After recrystallization from acetone, the crystals showed the typical transition to larger thin plates at 190° and melted at 210–212° (micro-block).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.42; H, 5.12; N, 14.95.

When this synthetic product was mixed with the "natural" pyrolysis product melting at 210–211.5°, the melting point of the mixture was 210–212° with the usual transition at about 190°.

The ultraviolet absorption spectra of the "natural" and synthetic products were identical. A maximum, $E_{1\%}$ 220–228 at 2885 Å., was observed.

(5) Kehrmann and Bahatrian, *Ber.*, **31**, 2399 (1898).

Acknowledgment.—The authors acknowledge the coöperation of Mr. W. A. Bastedo, Jr., and Dr. N. R. Trenner and their associates for the ultraviolet absorption spectra and the potentiometric titrations and of Mr. R. N. Boos and his associates for the microanalyses.

Summary

Streptidine was degraded to guanidine by oxidation with potassium permanganate, and the yield of guanidine showed that streptidine contains two guanido groups. On treatment with barium hydroxide solution, streptidine was converted stepwise into a neutral substance, strepturea, and a basic substance, streptamine. These alkali degradation products have the composition $C_8H_{16}N_4O_6$ and $C_6H_{14}N_2O_4$, respectively. Periodate oxidation studies and other information showed that streptidine is a 1,3- or 1,4-diaminotetrahydroxycyclohexane. Pyrolysis of hexaacetylstreptamine gave acetic acid, and an excellent yield of 2,4-diacetamidophenol and 5-acetamido-2-methylbenzoxazole.

On the basis of the accumulated evidence, streptidine is one of the meso forms of 1,3-diguanido-2,4,5,6-tetrahydroxycyclohexane. Strepturea and streptamine are the corresponding urea- and amine-like structures.

RAHWAY, NEW JERSEY RECEIVED FEBRUARY 9, 1946

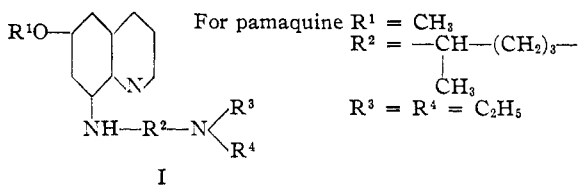
[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Two 6-β-Hydroxyethoxy-8-diethylaminoalkylaminoquinolines

BY MARCUS S. MORGAN AND LEONARD H. CRETCHER

Although pamaquine is a potent antimalarial, the Army[1] no longer advises its routine use for malaria therapy because the margin of safety between therapeutic and toxic doses is too small. In spite of recognized limitations, pamaquine possesses unique plasmodicidal action, namely, (a) gametocidal action on *Plasmodium falciparum*,[2] (b) reduction of the relapse rate in benign tertian malaria,[2] and (c) causal prophylactic activity at the toxic dose level as reported by James, *et al.*[3]

The present investigation was undertaken with the object of synthesizing analogs which would be less toxic to the host and yet retain the therapeutic activity of compounds of type I. In work previously published from this Laboratory, Cretcher and Pittenger propounded the principle of hydroxyalkylation[4] as a means of detoxification of some pharmacologically active compounds.



I

This principle was applied by Cretcher and associates[5] to a number of drugs and resulted in the discovery of the anti-pneumococcic drug, hydroxyethylapocupreine.[6] We therefore deemed it desirable to employ this approach in the synthesis of new pamaquine analogs.

Although the hydroxyl group has been introduced into the aliphatic side-chain (R^2) by several investigators[7] and recently 8-γ-hydroxypropyl-6-

(1) Surgeon General's Office, Circular Letter No. 153; *J. Am. Med. Assoc.*, **123**, 205 (1943).

(2) League of Nations, Fourth General Report of the Malaria Commission, Geneva, 1937, p. 120.

(3) James, Nicol and Shute, *Lancet*, [2], 341 (1931).

(4) Cretcher and Pittenger, THIS JOURNAL, **47**, 2560 (1925).

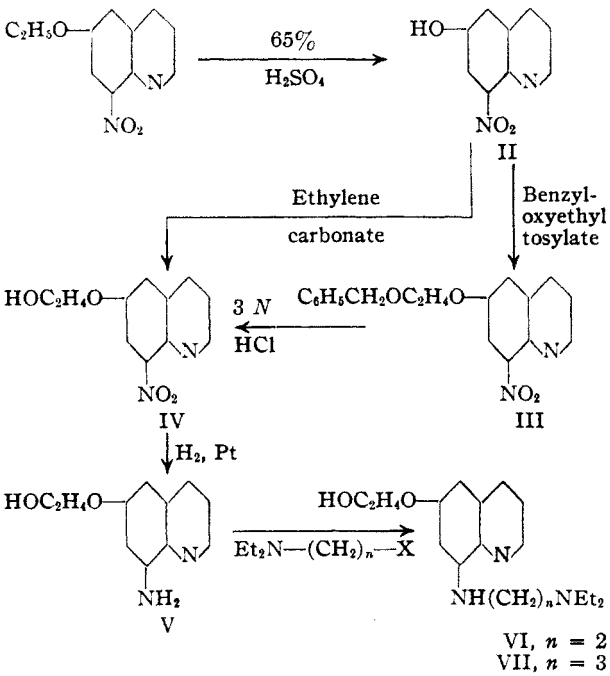
(5) For previous papers on hydroxyalkylation from this Laboratory, *cf.* THIS JOURNAL, **47**, 2560, 3083 (1925); **50**, 2758 (1928); **57**, 575 (1935); **59**, 227 (1937); **60**, 1473, 1582 (1938); **61**, 1783 (1939); **65**, 1092 (1943); *Chem. Rev.*, **30**, 49 (1942); *Chem. Eng. News*, **23**, 527 (1945).

(6) U. S. Patents 2,033,679 (March 10, 1936); 2,172,607 (Sept. 12, 1939).

(7) (a) Rohrmann and Shonle, THIS JOURNAL, **66**, 1643 (1944); (b) Magidson and Strukov, *Arch. Pharm.*, **271**, 569 (1933).

methoxyquinoline has been reported,[8] it would appear that, to date, the effect of hydroxyalkyl groups at position 6 has not been studied. Most of the research has dealt with variations in the side-chain in position 8, in which case R^1 has almost always been CH_3 or C_2H_5, with the exception of a few substances (*e. g.*, "Certuna") in which R^1 = H and one 6-butoxy derivative prepared by Baldwin and Robinson.[9] Magidson and Strukov[10] investigated the effect on the chemotherapeutic index of increasing the molecular weight of the alkyl group (R^1).

We now describe the preparation of 6-β-hydroxyethoxy-8-aminoquinoline (V) and two 8-ω-diethylaminoalkylamino derivatives thereof (VI and VII). 6-Ethoxy-8-nitroquinoline was prepared in 64% yield from 3-nitro-4-aminophenetole by the Strukov[11] modification of the Skraup reaction. On de-ethylation with sulfuric acid according to Magidson and Strukov,[10] crude 6-hydroxy-8-nitroquinoline (II) was obtained in 95% yield.



The purification of this compound, however, has not been previously described. Hydroxyethylation of II has been accomplished by two independent methods. The first (Method A) is based on the procedure reported from this Laboratory by Butler and Renfrew,[12a] employing benzyloxyethyl *p*-toluenesulfonate, thereby forming 6-benzyloxyethoxy-8-nitroquinoline (III) in 65% yield. On hydrolysis with 3 *N* hydrochloric acid, the benzyl group is split off as benzyl chloride to give 6-hydroxyethoxy-8-nitroquinoline (IV) in 97% yield. An improved technique has been devised wherein the acid solution is refluxed under a condenser with a Stark and Dean trap; thus the formation of benzyl chloride can be observed visually and the hydrolysis carried to completion. The second method (B) for hydroxyethylation is based on the more recently discovered method of Carlson[13] employing ethylene carbonate as the alkylating agent. Method B may be preferable because (a) of the high yields obtained, (b) of the ease of isolating the reaction product in the pure state, and (c) the hydroxyethyl group is introduced in one step.

The nitro compound IV was reduced to 6-hydroxyethoxy-8-aminoquinoline (V) by two methods; (A) by the use of ammonium sulfide according to the Magidson and Strukov[10] method for the reduction of the 6-alkoxy analogs, and (B) catalytic reduction with hydrogen in the presence of Adams platinum oxide catalyst in methanol suspension. Method B is preferred for small runs because (a) it is a one-step reaction which obviates the isolation of the intermediate hydrochloride and (b) of the higher yields obtained (90%, as compared with an over-all yield of 62% base by method A). The amine (V, the key intermediate for the synthesis of drugs of type I where R^1 = HOC_2H_4—) was isolated in the pure state by distillation *in vacuo*. Saturating a solution of V in absolute ethanol with anhydrous hydrogen chloride produced the monohydrochloride salt.

V was alkylated with the desired side-chain halide or its hydrohalide salt by a modification of the Rohrmann and Shonle[7a] procedure. Condensation of V with β-diethylaminoethyl bromide hydrobromide gave 6-β-hydroxyethoxy-8-(β-diethylaminoethylamino)-quinoline (VI), and with γ-diethylaminopropyl chloride gave 6-β-hydroxyethoxy-8-(γ-diethylaminopropylamino)-quinoline, (VII). These compounds were isolated as the dihydrochlorides in which form they are suitable for pharmacological study. The absence of unalkylated amine (V) in the final drugs was confirmed by an adaptation of the test proposed by Ballard and Pierce[14] for the determination of 6-methoxy-8-aminoquinoline in the assay of pamaquine.

Further derivatives of V and other 6-hydroxyalkyl analogs are in the process of synthesis and will be reported on at a later date.

Experimental

6-Ethoxy-8-nitroquinoline was synthesized from 3-nitro-4-aminophenetole (Eastman) by the Strukov[11] modification of the Skraup reaction. In a typical experiment employing 400 g. of glycerol, 130.5 g. of arsenic pentoxide, 200 g. (1.1 moles) of 3-nitro-4-aminophenetole and 324 g. (in two portions) of concentrated sulfuric acid, the yield

(8) Crum and Robinson, *J. Chem. Soc.*, 561 (1944); Yanko, Mosher and Whitmore, THIS JOURNAL, **67**, 664 (1945).

(9) Baldwin and Robinson, *J. Chem. Soc.*, 1264 (1934).

(10) Magidson and Strukov, *Arch. Pharm.*, **271**, 359 (1933).

(11) Strukov, *Org. Chem. Ind., U. S. S. R.*, **4**, 527 (1937); *C. A.*, **32**, 4987 (1938).

(12) (a) Butler and Renfrew, THIS JOURNAL, **60**, 1473, 1582 (1938); (b) compare Tipson, Clapp and Cretcher, *ibid.*, **65**, 1092 (1943).

(13) Carlson and Cretcher, forthcoming publication.

(14) Ballard and Pierce, *Quart. J. Pharm. Pharmacol.*, **17**, 30 (1944).

of crude product was 201 g. (84%). After recrystallization from ethylene dichloride, there was obtained 154.3 g. (64% of the theoretical) of yellow crystals, m. p. 158.5–160° (Magidson and Strukov,[10] m. p. 158°).

6-Hydroxy-8-nitroquinoline (II).—The de-ethylation was carried out according to the method of Magidson and Strukov.[10] 6-Ethoxy-8-nitroquinoline (129.5 g.) was dissolved in diluted sulfuric acid (prepared by adding 423 g. of concentrated sulfuric acid to 227 g. of water) and the reaction mixture heated at 120° (internal temp.) during twenty-four hours, followed by refluxing at 139–140° (internal temp.) during twenty hours. In order to reach a reflux temperature of 140°, it was necessary to remove the condenser temporarily and permit some steam to escape. The yield was 107.1 g. (95%); m. p. 228–229° (dec.). Magidson and Strukov,[10] m. p., 230° (dec.), made no mention of purification.

For purification, the crude product (50 g.) was extracted with boiling acetone (1 liter) and the filtrate evaporated to yield a buff-colored material (m. p. 236–237° dec.) suitable for subsequent alkylation. For analysis, a sample was recrystallized from pyridine–water in the form of light-greenish, fluorescent crystals, m. p. 236.5–237° (dec.).

Anal.[15] Calcd. for $C_9H_6N_2O_3$: C, 56.84; H, 3.18; N, 14.73. Found: C, 56.97; H, 3.05; N, 14.38.

6-Hydroxyethoxy-8-nitroquinoline (IV). A. Method Employing Benzyloxyethyl Tosylate.[12] 6-Benzyloxyethoxy-8-nitroquinoline (III).—To a solution of 3.5 g. of solid potassium hydroxide (85%) in absolute ethanol (150 ml.) was added 10 g. of 6-hydroxy-8-nitroquinoline (II), and 16.1 g. (1.0 equiv.) of benzyloxyethyl tosylate.[16] The solution was heated under reflux in a boiling water-bath for three hours. The cold suspension was diluted with an equal volume of chloroform, filtered and the filtrate evaporated to dryness under reduced pressure. The brown, amorphous residue was dissolved in chloroform (150 ml.), filtered and extracted with 10% sodium hydroxide solution. The combined chloroform extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. The brown, crystalline residue weighed 15 g. (90%).

The crude 6-benzyloxyethoxy-8-nitroquinoline was purified by extraction with hot carbon tetrachloride and after filtering from a small amount of insoluble matter gave buff-colored crystals; m. p. 97.5–98.2°, in 65% yield.

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.65; H, 4.97; N, 8.64. Found: C, 66.60; H, 5.00; N, 8.90.

Hydrolysis of III to IV.—6-Benxyloxyethoxy-8-nitroquinoline (8.0 g.) was dissolved in 400 ml. of 3 *N* hydrochloric acid and refluxed under a condenser connected through a Stark and Dean trap. The benzyl chloride collected in the bottom of the trap and after eight hours of refluxing constituted 95% of the theoretical amount. The cold acid solution (from the flask only) was extracted with 96% ether to remove traces of benzyl chloride, and rendered strongly alkaline to phenolphthalein with 50% sodium hydroxide solution (70 ml.). The light yellow, flocculent product was thoroughly washed with water and dried in a vacuum desiccator over phosphorus pentoxide. The yield was 5.6 g. (97%), m. p. 161–163°. 6-Hydroxyethoxy-8-nitroquinoline (3.0 g.) was crystallized from hot ethylene dichloride (80 ml.) giving light-yellow needles (2.6 g.), m. p. 163.5–164.5°. There was no depression of the melting point on admixture with a sample, having the correct analysis, prepared by Method B.

In an experiment where the 3 *N* hydrochloric acid solution was merely heated under reflux in a boiling water-bath[12b] during four hours, only partial hydrolysis resulted, and pure IV was not readily isolated.

B. Method Using Ethylene Carbonate.[13]—Ethylene carbonate was prepared[17] by ester interchange[18] (alcoholysis) between ethylene glycol and diethyl carbonate in the presence of an alkaline catalyst. The most rapid and efficient method developed for the preparation of reasonably large quantities was the following. The apparatus consisted of a 2-liter flask fitted with a thermometer and glycol-sealed mechanical stirrer, and connected to a 15-inch, insulated Vigreux column. A mixture of 335 ml. (6 moles) of ethylene glycol and 800 ml. (6.6 moles) of diethyl carbonate was heated, with constant stirring, until the two immiscible layers were mutually dissolved (internal temp., 100–105°). The stirrer was then removed, 0.3 g. of anhydrous potassium carbonate and some boiling chips quickly added and the flask closed. A rapid evolution of ethanol soon commenced and distillation was maintained at a rapid rate by gradual increase of temperature. The temperature at the top of the column was kept below 80°; the total volume of distillate (ethanol) represented 98% of theoretical. The cooled residue was dissolved in 300 ml. of absolute ethanol, filtered, and the filtrate cooled in an ice-bath, whereupon crystallization took place. After thorough cooling, the crystals were filtered off on a precooled Büchner funnel with the aid of a rubber dam, and washed with two portions of 96% ether.

Two such crops (from 12 moles of glycol) were united and recrystallized from absolute ethanol (400 ml.). The crystals were washed with absolute ether and dried in a vacuum desiccator over phosphorus pentoxide. The yields generally varied from 51 to 55%; by working up the mother-liquors the yield was raised to 64%.

6-Hydroxyethoxy-8-nitroquinoline (IV). Method B.—A mixture of 6-hydroxy-8-nitroquinoline (52.4 g., 0.275 mole) anhydrous potassium carbonate (57.1 g., 0.413 mole, 1.5 equiv.), and ethylene carbonate (242 g., 2.75 moles) was placed in a 3-necked, 1-liter flask fitted with a mercury-sealed stirrer, thermometer, and a condenser closed by a "drierite" tube. With continuous mechanical stirring, the mixture was heated at 95 ± 2° (reaction temp.) during two hours. The cooled reaction product was diluted with 250 ml. of water, and, after thorough agitation, the light brown product was filtered off. The residue was dissolved in 5 *N* hydrochloric acid (225 ml.), the resulting solution thoroughly cooled in an ice-bath, and a solution of sodium hydroxide (25%) added dropwise with continuous stirring. (If the precipitate first formed is viscous or resinous, it is best to stop the addition of alkali and stir the product until it becomes a workable solid; the remainder of the alkali is then added until the solution is strongly alkaline to phenolphthalein. Some gas evolution may be observed near the end of the neutralization.) The precipitate was filtered off, washed thoroughly with water, and dried in a vacuum oven at 60°. Yield of crude product was 61.4 g. (95%), m. p. 158.5–161.5° (sintered at 156°).

The crude product (15 g.) was suspended in absolute ethanol (450 ml.) and boiled with Nuchar under reflux for ten minutes. The hot suspension was filtered, and the filtrate on cooling slowly deposited light tan-colored crystals, m. p. 162.5–163.5°, in 86.4% of the theoretical yield; recrystallized sample had a m. p. 164–165°.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.30; H, 4.23; N, 11.87.

6-Hydroxyethoxy-8-aminoquinoline (V). Method A.—The reduction of the 8-nitro to the 8-amino group was first carried out with ammonium sulfide according to the procedure described by Magidson and Strukov[10] for the 6-alkoxy analogs, and the hydrochloride isolated in 86% yield from the ethanol filtrate. The free base was liberated with cold sodium hydroxide and extracted with chloroform. The dried chloroform solution was evaporated and the residue distilled at 170–175° at 0.15 mm. as a pale yellow, viscous liquid. After solidification (or crystallization induced by scratching) it had m. p. 108–109.5°. The yield, based on 8-nitro compound, was 62%.

Method B.—The nitro compound (9 g.) was suspended in 100 ml. of methanol, 0.1 to 0.2 g. of Adams platinum oxide catalyst added, and the reduction carried out with hydrogen in the Burgess–Parr apparatus at room temperature. The initial pressure was 41 to 42 lb. per sq. in., the

(15) Most of the microanalyses were performed by Dr. Carl Tiedcke, New York, N. Y.

(16) Clapp and Tipson, THIS JOURNAL, in press.

(17) In collaboration with Dr. W. W. Carlson of this Department.

(18) Carothers and Van Natta, THIS JOURNAL, **52**, 314 (1930).

absorption of hydrogen was quite rapid, and the reduction was complete in one hour. Since the amine V is very soluble in methanol, the reduction can be followed by the dissolution of suspended nitro-compound. The rate of reduction was approximately 3.5 times as rapid in methanol as in ethanol. The catalyst was filtered off and the filtrates from several reductions combined and concentrated to a small volume. After evaporation of the methanol and water, the dark-red viscous residue was distilled *in vacuo*, and the fraction boiling at 179–180° (0.15–0.2 mm.) was collected; the pale yellow crystals had m. p., 108–109.5° (yield 90% of the theoretical).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.93; N, 13.72. Found: C, 64.57; H, 5.68; N, 13.61.

6-Hydroxyethoxy-8-aminoquinoline Monohydrochloride.—Addition of an excess of dry hydrogen chloride to a cold solution of 4.5 g. of the base (V) in 200 ml. of absolute ethanol produced a copious, bright yellow precipitate. The dried product weighed 5.1 g. (96%) and had m. p. 218–220° (dec., darkened at 215°).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$·HCl: N, 11.64; Cl, 14.73. Found: N, 11.60; Cl, 15.50.

γ-Diethylaminopropyl chloride was isolated in 76% yield by the method of Gilman and Shirley,[19] as a colorless liquid boiling at 66–68° at 21 mm. (distilled from glass wool); $n^{20}D$ 1.4397. This halide was stored in a refrigerator (0–5°) for six months with practically no change ($n^{20}D$ 1.4405).

6-β-Hydroxyethoxy-8-(γ-diethylaminopropylamino)-quinoline Dihydrochloride (VII) (SN-11,660[20]).—A mixture of 10 g. (0.049 mole) of 6-β-hydroxyethoxy-8-aminoquinoline, 8.42 g. (1.15 equiv.) of γ-diethylaminopropyl chloride, and 35 ml. of absolute ethanol was heated under reflux in a thermostatically-controlled glycerol bath at 90–92° for forty-eight hours.[7a] The cooled reaction product was diluted with water to about 100 ml. and extracted with chloroform to remove any unreacted amine. The aqueous layer was cooled by the addition of chopped ice, rendered alkaline by the addition of an excess of cold potassium carbonate solution (30 g. in 40 ml. of water), and the free base extracted with chloroform. The chloroform extract was dried with Drierite, filtered and the filtrate evaporated to dryness under reduced pressure to give a dark red, viscous residue weighing 14.2 g. A cold solution of this base in absolute ethanol (75 ml.) was treated with an excess of dry hydrogen chloride; cooling in the refrigerator overnight produced a crop of orange-colored crystals (7.9 g.) which was filtered off with the aid of a rubber dam and dried in a vacuum desiccator over phosphorus pentoxide and soda-lime. On evaporating the filtrate to dryness several times with additional ethanol, a second crop was obtained.

For recrystallization, crop I was dissolved in 75 ml. of hot absolute ethanol, filtered at room temperature, the filtrate brought to the boil under reflux and hexane (b. p. 60–70°) added to incipient turbidity; the solution deposited beautiful yellow needles on cooling. The yield was 7.0 g., m. p. 179–180.5°.

Anal. Calcd. for $C_{18}H_{27}N_3O_2$·2HCl: N, 10.76; Cl, 18.16. Found: N, 10.33; Cl, 17.80.

6-β-Hydroxyethoxy-8-(β-diethylaminoethylamino)-quinoline Dihydrochloride (VI) (SN-11,220).—The amine (V) was alkylated with β-diethylaminoethyl bromide hydrobromide but, although the dihydrobromide began to crystallize out of solution after four hours, the alkylation was run for forty-eight hours and the **dihydrochloride** was isolated in 71.5% yield. The yellow, hygroscopic needles had m. p. 225° (sintered at 213°).

For analysis, 2 g. of the product was recrystallized from a minimum of boiling absolute ethanol (55 ml.), resulting in 1.2 g. of yellow crystals, m. p. 226.5–227.5° (sintered at 217°).

Anal. Calcd. for $C_{17}H_{25}N_3O_2$·2HCl: C, 54.26; H, 7.23; N, 11.17; Cl, 18.84. Found: C, 53.66; H, 7.11; N, 10.70; Cl, 18.88.

In another run the crystalline **dihydrobromide** was isolated directly in 70% yield by filtering the ethanol suspension and washing the crystals with ethanol. This salt was recrystallized from hot ethanol (5 g. in 350 ml.) giving fine, yellow needles; m. p. 229–231°.

Anal. Calcd. for $C_{17}H_{25}N_3O_2$·2HBr: N, 9.03; Br, 34.4. Found: N, 9.42; Br, 34.6.

Test for Presence of Unalkylated Primary Amine.—A small amount (about 0.01 to 0.05 g.) of the substituted 8-aminoquinoline salt (*e. g.*, VI or VII) is dissolved in about 5 ml. of water and rendered acid to congo red. One ml. of 1 *N* hydrochloric acid is added and the solution cooled in an ice–water-bath. Two ml. of cold 2.5% sodium nitrite solution is then added and the solution allowed to stand for five minutes in an ice-bath. A second solution is prepared from 2.5 ml. of 5% sodium carbonate and 0.3 ml. of 1.7% (0.05 *N*) R salt (disodium 2-naphthol-3,6-disulfonic acid). The cold, diazotized solution is then added to the alkaline solution of R salt and the color observed after the elapse of thirty minutes. Tests with a blank and a control with a very small amount of amine (V) are simultaneously carried out.

The amine produced a very deep red-colored solution, whereas compounds VI and VII produced an amber to light brown-colored solution. This test might be useful for following the course of an alkylation and also as a control on the purification procedure.

Summary

1. 6-β-Hydroxyethoxy-8-nitroquinoline (IV) has been prepared by two methods; (A) through the hydrolysis of the benzyloxyethyl ether, and (B) directly by alkylation of 6-hydroxy-8-nitroquinoline with ethylene carbonate.

2. 6-β-Hydroxyethoxy-8-aminoquinoline (V) has been obtained in 90% yield from IV by catalytic reduction (Adams platinum oxide) in methanol suspension.

3. Two new 6-β-hydroxyethyl analogs of the pamaquine series have been synthesized by alkylation of V with ω-diethylaminoalkyl halides.

PITTSBURGH 13, PA. RECEIVED JANUARY 19, 1946

(19) Gilman and Shirley, THIS JOURNAL, **66**, 888 (1944).

(20) The survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of these compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.